

## Book Review

D.L. Price, H. Thoenen, A.J. Aguayo (Eds.) *Neurodegenerative Disorders Mechanisms and Prospects for Therapy*, John Wiley & Sons, Chichester, England, 1991, 301 pp.

This book is a report of a Dahlem workshop held in Berlin in August 1990. The format followed in the workshop and published in these proceedings was to review four topics in a series of background papers and then to provide a group discussion intensively examining the issues in each area. The four topics included: (1) The mechanisms of neuronal dysfunction and death including (a) genes involved in neuron cell death in *C. elegans*, (b) the role of excitotoxicity in neuronal damage, (c) the role of calcium in cell death, and, (d) cell death induced by neurotrophic factor withdrawal. (2) The molecular pathology of Alzheimer's disease and prion diseases in both of which encephalopathy results from deposition of amyloid in neural parenchyma. In Alzheimer's disease the amyloid derives from the A<sub>4</sub> peptide fragment of the normal host amyloid precursor protein, while in the prion-induced spongiform encephalopathies, the amyloid fibrils derive from post-translational modification of the normal cellular prion protein isoform. (3) Biological events critical in development, regeneration, and repair, with emphasis on axonal outgrowth and guidance as well as target recognition, synapse formation and stabilization. (4) Therapeutic strategies to enhance neuronal survival and repair with neurotrophic factors and to enhance functional recovery with neural implants and genetically modified cells.

At the time that this conference was held, the papers and discussions of the many internationally distinguished scientists certainly represented the most comprehensive and succinct delineation of the cellular and molecular neurobiological principles of possible relevance to these disorders. Even two years later these concepts are of considerable value to any serious student of these disorders; and these proceedings provide one of the best surveys of strategies to approach the problems of neuronal cell death. As would be anticipated in any field moving so quickly, much new data have become available which are not represented in this volume. For example, a plea is made for animal models of human disease and the value of the transgenic approach. In 1991, three transgenic models of amyloid

accumulation were described which provided significant credibility to Masters and Beyreuther's contention that the formation of  $\beta$  A<sub>4</sub> amyloid from amyloid precursor protein could be a 'proximal' cause of Alzheimer's disease. Before we chide the editors for not including an addendum to these proceedings, we should also note that even more recently two of the three models have been retracted, one because the experiments were not reproducible, and the other because control animals also had reactivity with purportedly specific amyloid antibodies. Thus, perhaps the moral should be that conferences should be published late rather than on time. Nevertheless, the  $\beta$  A<sub>4</sub> amyloid should be, and is, still considered a likely contributor to neuronal damage in Alzheimer's disease.

Among the more interesting papers is a discussion of mutations which give rise to cell death in the nematode. Horvitz and Chalfie describe two genes (*ced-3* and *ced-4*) which act to cause cell death and mutations that block their activity prevent cell death. Another gene (*ced-9*) appears to antagonize the actions of *ced-3* and *ced-4*; and mutations that increase *ced-9* function can prevent programmed cell death. Such data suggest the presence of molecules which might prevent cell death in neurodegenerative diseases. Whether these molecules are neurotrophic factors acting in a neuroprotective role (another concept receiving increasing attention since this conference was held) is presently unclear. The central importance of calcium in cell death and the many different pathways through which cell damage could be produced are also carefully delineated in the volume. What is not presented is our current understanding of the process of cell death called apoptosis which plays a role in programmed cell death. Understanding the mechanism of apoptosis may help us understand cell death in neurodegenerative diseases.

It is surprising that a volume dedicated to understanding mechanisms of neurodegenerative disorders would focus only on Alzheimer's disease and spongiform encephalopathies, and not provide background papers or detailed discussion on, at the very least, Parkinson's disease and amyotrophic lateral sclerosis. The concept of selective vulnerability suggests different mechanisms for neuronal damage and death in different diseases. The presence of increased  $\beta$  A<sub>4</sub> may well explain neuronal cell damage in Alzheimer's disease, but is less likely to help us understand the mechanism

of substantia nigra damage in Parkinson's disease where a detailed knowledge of free radical generation and nigral cell sensitivity may be required. Similarly, other pathways and mechanisms are likely to be involved in explaining motoneuron damage in amyotrophic lateral sclerosis. Without a detailed understanding of the mechanisms of selective vulnerability of neurons affected in these other neurodegenerative diseases, the prospects for meaningful therapy may be somewhat more limited.

Nevertheless, this volume does provide a commendable survey of the general neurobiological principles of

neuronal development and maintenance, and discusses how such concepts as well as current theories of excitotoxicity, prion diseases and neural transplants may help us approach the problems of neurodegenerative disease. It is both informative and useful.

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